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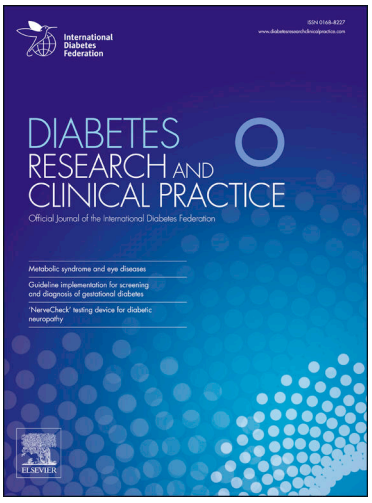
Published in:
Diabetes Research and Clinical Practice

DOI (link to publication from Publisher):
10.1016/j.diabres.2019.107997

Publication date:
2020

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

Journal Pre-proofs



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PII: S0168-8227(19)31182-9
DOI: https://doi.org/10.1016/j.diabres.2019.107997
Reference: DIAB 107997

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 19 August 2019
Revised Date: 13 December 2019
Accepted Date: 30 December 2019

Please cite this article as: K. Aasbjerg, C. Holm Nørgaard, N. Vestergaard, P. Søgaard, L. Køber, P. Weeke, G. Gislason, C. Torp-Pedersen, Risk of diabetes among related and unrelated family members, *Diabetes Research and Clinical Practice* (2019), doi: https://doi.org/10.1016/j.diabres.2019.107997

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1.4 Word count (of both Abstract and main text).

3418

2 Abstract

2.1 Aims

The aim was to explore familial aggregation of diabetes in genetically related and unrelated individuals.

2.2 Methods

We included citizens from Danish nationwide registries between 1995-2018 and calculated rate ratios (RR) of diabetes based on family relation using Poisson regression.

2.3 Results

Of 7.3 million individuals eligible for inclusion, we identified 343,237 (4.7%) with diabetes. The RR of diabetes was 2.02 (95% CI: 1.99–2.05; p<0.0001) if any relative had diabetes, 1.79 (95% CI: 1.76–1.83) if a father had diabetes, and 2.06 (95% CI: 2.02–2.10) if a mother had diabetes. If both parents had diabetes, the RR was 3.40 (95% CI: 3.24–3.56). Among full siblings, the RR for developing diabetes was 2.77 (95% CI: 2.71–2.84) and 5.76 (95% CI: 5.00–6.63) for twins. For second-degree relatives, half siblings with a common mother had a RR of 2.35 (95% CI: 2.15–2.56), and with a common father 1.99 (95% CI: 1.81–2.17). Furthermore, the RR was 1.60 (95% CI: 1.56–1.64) if a wife had diabetes, and 1.41 (95% CI: 1.38–1.44) if a husband had diabetes. A subgroup analysis of individuals receiving insulin only treatment (N=23,054) demonstrated a similar risk pattern, although with slightly higher risk estimates.

2.4 Conclusions/interpretation

Family aggregation of diabetes is associated with genetic disposition with maternal status being the predominant factor. Furthermore, we observed increased risk of diabetes in second-degree relatives, and between unrelated spouses, indicating that environmental factors influence diabetes risk substantially.

2.5 Keywords

Diabetes, heredity, epidemiology, genetic factors, environmental factors

2.6 Abbreviations

Aside from the standard abbreviations in Diabetologia (http://www.diabetologia-journal.org/webpages/styleguide/abbreviations.html) no abbreviations were used.

There has been a massive global increase in type 2 diabetes along with a small but surprising rise in type 1 diabetes [1,2]. While diabetes is reaching pandemic status, the familial contribution to the development of diabetes is not well understood and to what extent it derives from shared genetics versus environment. Previous studies have found that the risk of type 2 diabetes is at least two times higher in individuals with one parent with diabetes and up to four times higher with two parents with diabetes [3,4]. Furthermore, the concordance rate of type 2 diabetes has been shown to be higher in monozygotic versus dizygotic twins [5–7]. Despite these associations, efforts to determine a clear genetic cause of type 2 diabetes have been troublesome. Genome-wide association studies have led to the identification of more than 100 genetic loci, each tied to a small but increased susceptibility of developing type 2 diabetes [8]. However, this polygenic understanding of type 2 diabetes captures only up to 10 percent of familial aggregation of the disease [9]. Furthermore, even among groups with a genetically increased risk of diabetes, environmental factors play a key role for diabetes development, as exemplified by the Mexican Pima Indians, among who there is less than one-fifth of the type 2 diabetes prevalence compared to Pima Indians in the Unites States[10]. Additionally, multivariable modelling has shown that lifestyle and genetic factors predict development of type 2 diabetes with similarly high accuracy [11]. In contrast, almost half of the familial aggregation in type 1 diabetes can be ascribed to known loci [12]. However, hereditability in type 1 diabetes is less distinct as more than 90 percent of patients with type 1 diabetes does not have a first-degree relative with the disease. Nonetheless, the lifelong risk of type 1 diabetes has been found to be significantly increased in those who have a relative with type 1 diabetes compared to having no family history, and the concordance rate among identical twins is approximately 50 percent [5,13].

It is unclear to which extent this familial aggregation is based on genetics and which part is environment. To further detangle this, we performed a study on familial aggregation of diabetes in Denmark including both related and unrelated individuals.

4 Methods

4.1 Study population

In Denmark, all citizens are at birth assigned a unique and permanent personal identification number (civil registration number) that is used throughout all private and public sectors to identify individuals. All healthcare and governmental institutions as well as pharmacies are required by law to register data on individuals using the civil registration number, enabling direct linkage of various registries and data sources containing anonymized data.

The present study included patients with new-onset diabetes from January 1, 1995 to December 31, 2018 and their family relations, as listed in the Danish nationwide registries. Specifically, we used a combination of data on drug prescriptions (The Danish National Prescription Registry [14]) , causes of death (The Danish registers of causes of death [15]), immigration and family relations (The Danish Civil Registration System [16]) to calculate the risk of developing diabetes based on paternal, maternal, sibling, half-sibling, and marital status. Individuals who were adopted or had incomplete immigration data were excluded.

4.2 Definition of diabetes

Diabetes was defined by the claim of at least two prescriptions of a glucose-lowering drug (Anatomical Therapeutic Chemical Classification (ATC) A10), starting from the day of the last prescription in the first quarter (90 days) with at least two prescriptions.

To ensure that only individuals with new-onset diabetes were included, anyone claiming a prescription of a glucose-lowering drugs within the first study year January 1, 1995 to December 31, 1995) was excluded.

Furthermore, we defined a type 1 diabetes subgroup (“type 1 subgroup”) including individuals, who solely claimed prescriptions of insulin (ATC A10A) during the study period.

4.3 Definition of family relations

Family relations were identified using the The Danish Medical Birth Registry, which lists all individuals born in Denmark, including the identity of the father and/or mother, if known. Population groups of interest were identified as follows: a) any family member has diabetes (second degree relatives being the most remote member identified from registries), b) father has diabetes, c) mother has diabetes, d) both parents have diabetes, e) half-sibling (common father) has diabetes, f) half-sibling (common mother) has diabetes, g) full sibling has diabetes, h) wife has diabetes, and i) husband has diabetes (wife and husband were defined by having a common child).

4.4 Statistical methods

Individuals were included in the study if they were alive during 1995–2018 and not diagnosed with diabetes prior to January 1, 1996. Individuals were followed until death, immigration from Denmark or until 31 December 2018. For the time dependent analyses, individuals were split first by individual diabetes diagnosis date, then by diagnosis date of family relation (mother, father, sibling etc.) resulting in dichotomous variables for each risk profile, and finally by age and calendar time both in five-year intervals.

Rate ratios (RR) of diabetes incidence and associated p-values were calculated using Poisson regression models that included, age, calendar time and familial diabetes by mother, father, half- and full-siblings

The rate (prevalence) of diabetes in the total population was calculated and stratified by year, age, and sex. Likewise, the rate of diabetes was calculated for each sub-population of interest, e.g. children with mothers/fathers with diabetes, half- and full-siblings etc.

Results were reported as total population at risk, population diagnosed, percent diagnosed, RR with 95% confidence interval (95% CI) as well as p-values were reported. A p-value of less than 0.05 were considered significant.

To evaluate the model assumption of constant risk in time intervals, we examined individuals in one-year intervals of age, instead of the original five-year intervals. No overall difference in incidence rate ratios were observed.

All statistical analyses were carried out using SAS version 9.4 (SAS Institute Cary, North Carolina, USA).

4.5 Ethical considerations

Registry based studies does not require ethical approval in Denmark. The project was approved by the Danish Data Protection Agency, approval no. P-2019-382.

5 Results

In total, 10,052,539 individuals were identified from the Danish registries in the period 1995–2018 and considered eligible for inclusion in the study. Of these, 2,759,704 were excluded due to immigration, death prior to inclusion (1 January 1996), or incomplete data, resulting in a total study population of 7,292,835 individuals. Of these, a total of 343,237(4.7%) were diagnosed with diabetes (1996-2018). The selection of the study population is illustrated in Figure 1.

Baseline demographics are displayed in Table 1. The mean age at diabetes onset was 59.4 years with 90% of individuals between 28.0 and 78.9 years, and no significant difference was observed between males (N= 175,894) and females (N= 167,373).

The Birth Registry contained data on 4,423,476 childbirths, of which 4,070,681 (92,0 %) had data on both parents, 24,423 (0.6%) had data on the father only, and 328,372 (7,4%) on the mother only.

5.1 Risk of diabetes onset

The multivariable Poisson regression analyses were adjusted for calendar time in periods of five years, age, and sex and are presented in Figure 1.

Considering diabetes status, a total of 619,746 (8.5% of all) were at risk for diabetes based on any family member with diabetes, of which 36,858 (5.9%) were diagnosed with diabetes during the study period (RR 2.02; p<0.0001). For individuals with a diabetic father, 5.1% out of 297,441 at-risk individuals developed diabetes (RR 1,79; p<0.0001), for individuals with a diabetic mother, 6.3% out of 250,140 at-risk individuals developed diabetes (RR 2.06; p<0.0001), and 9.6% out of 33,224 at-risk individuals with both parents being diabetic developed diabetes during the study period (RR 3,40; p<0.0001). The risk of developing diabetes was significantly higher for maternal as compared to paternal relation (p<0.0001).

Of 99,600 individuals with a diabetic wife, 14.4% developed diabetes (RR 1.60; p<0.0001), whereas only 10.5% of 140,071 individuals with a diabetic husband developed diabetes during the study period (RR 1.41; p<0.0001).

Of 121,357 full siblings at risk, 11.1% developed diabetes (RR 2.77; p<0.0001), whereas only 5.4% and 6.6% of half-siblings with a common father or mother, respectively, developed diabetes (RR 1.99 and 2.35; p<0.0001). For twins, 21.2% out of 1,704 at-risk developed diabetes (RR 5.76; p<0.0001). It was not possible to distinguish identical and fraternal twins from the Registries.

All analyses were repeated in the type 1 subgroup (Figure 3), which included 23,054 individuals (0.3%). All population groups were found to be associated with a statistically significant elevated risk of diabetes.

In the type 1 subgroup, the greatest risk was observed among individuals with a diabetic twin (RR 39.77; p<0.0001), followed by individuals with both parents being diabetic (note that only 3 individuals were included in this group; RR 9.33; p=0.026), individuals with a diabetic sibling (RR 10.56; p<0.001), a diabetic mother (RR 4.48; p<0.0001) or father (RR 3.23; p<0.0001).

A subgroup analysis of males and females at risk of developing diabetes based on one or more diabetic parents were performed. For females with a diabetic mother was 1.97 (95% CI: 1.92–2.02; p<0.0001), a diabetic father 1.74 (95% CI: 1.70–1.79; p<0.0001) and if both were diabetic 3.24 (95% CI: 3.05–3.45; p<0.0001). Similarly for males the RR was 2.19 (95% CI: 2.12–2.25; p<0.0001) 1.85 (95% CI: 1.80–1.91; p<0.0001) and 3.61 (95% CI: 3.37–3.88; p<0.0001). See also Figure 4.

The subgroup analysis was further expanded by including an analysis of males and females with a parent >60 years of age at diabetes onset. The RR for males with fathers (>60) were 1.58, and for males with mothers (>60) RR was 1.71. Similarly for females with fathers (>60) RR was 1.62 and for females with mothers (>60) RR was 1.77.

6 Discussion

In this nationwide study we examined the risk of developing diabetes in offspring and spouses of more than 300,000 individuals with diabetes, we demonstrate a strong familial clustering regarding both genetic as well as non-genetic (second degree relatives and spouses) relations. Hence, our findings suggest that both genetic and environmental factors have predictive value regarding the risk of developing diabetes. Surprisingly, the results were consistent in a subgroup of individuals with type 1 diabetes, although with lower statistical significance, owing to the smaller sample size (23,054 in the type1 group vs. 343,237 in the any diabetes group).

Overall, the risk of developing diabetes increased with the number of family members with diabetes; the strongest risk was associated with children, where both parents had diabetes, as well as twins with a diabetic sibling.

Similarly, the risk increased for individuals with a genetically unrelated family member with diabetes, such as a second-degree relatives and spouses. Subgroup analysis of males vs. females, and diabetic parents below/above 60 years of age showed similar results.

Altogether we believe our findings indicate that both genetic factors play a for the risk of developing diabetes, as well as environmental factors, indicated by the associations found in the examined groups of individuals with no known common genetic dispositions (spouses, thus environmental factors) and groups with varying degrees of common genetic inheritance (half and full siblings as well as twins, thus a combination of environment and genetic factors). As environmental factors are included in all of the examined subgroups, a predominant environmental influence cannot be completely ruled out, although the higher risk associated with increased common genetic inheritance (from half siblings to twins) suggests that genetic risk plays and a role as well (Figure 2).

6.1 Comparison with other studies

Our results are in line with a previous study from Sweden studying familial aggregation which found comparable rates of diabetes in relation to full sibling, mothers, and fathers. The study also found an increased rate of diabetes among half-siblings and non-related family members, including spouses. However, adoptees did not have an increased risk of diabetes in relation to their adopted parents, whereas they had an increased risk in relation to their biological parents [17]. Our risk estimates were also comparable to a US study examining the RRs for first-degree relatives with type 1 and type 2 diabetes [18]. A Finnish study investigated the risk of diabetes given a family history of diabetes, which was associated with a significantly increased hazard ratio of 2.2, further supporting family history as a strong predictor of diabetes risk [19].

Several studies have identified specific genes associated, or potentially associated, with diabetes[9,20] some of these indirectly as risk factors of obesity[21].

Meigs et al. demonstrated that known genetic risk factors only had a slightly increased predictive value of diabetes, as compared to common non-genetic risk factors [22]. This study is not in conflict with our findings, as Meigs et al. focused on known genetic factors. Our data on the other hand, focused on known family relations thus including all genetic risk factors, known as well as unknown, in our study which indicated similar overall conclusions.

Similarly in a recent study by Poveda et al., genetic risk factors and lifestyle risk factors contributed evenly to the risk of developing diabetes [23], but again only known genetic risk factors were examined. A similar conclusion was reached by Lyssenko et al. [24]. Overall the studies attempting to predict diabetes based on clinical risk factors and genetic factors are vulnerable due to the relatively low predictive value of the known genes, which in turn could indicate that the genes examined are not the most significant risk factors [25]. It should be noted that Bothe the study by Poveda and Meigh only focused on type 2 diabetes.

Our results might be in conflict with a study by Knowler et al. regarding intervention with lifestyle versus metformin [26]. In the study by Knowler et al. , the authors demonstrate that lifestyle intervention is a much stronger intervention to prevent the onset of diabetes, than metformin treatment, in individuals with elevated fasting glucose. However, the study included 'high-risk' individuals with high fasting glucose levels, which in turn could indicate genetic disposition, whereas our study could be interpreted as genetic factors are predominant in the overall risk.

6.2 Strengths and weaknesses of the study

A major strength of the present study is the number of eligible study participants, which are well above six million. The Danish National Registries are reliable sources of data [27,28], and due to the number of individuals anyone with unreliable or incomplete (missing) data can be readily excluded.

The most obvious bias in this kind of study would be selection bias, e.g. the validity of the data in the registry. Based on several other studies[27,29], the Danish National registries are a very valid source of information[14], and therefore we consider the selection of individuals as valid. By including the entire population of Denmark, we avoided any selection bias related to age, sex, income, willingness to participate, relation to a physician, or health insurance organizations.

However, although the National Prescription Registry contains information on all prescribed drugs, the indication for the prescription is not available. Consequently, any drug prescribed for a different reason than blood glucose lowering due to diabetic status, could lead to a wrong conclusion. However, as the overwhelming majority of glucose lowering drugs only is prescribed to diabetic individuals, we consider the risk of miss-diagnosis negligible in the current context.

With regards to the definition of type1 vs. type2 diabetes, our definition of type2 based on any other glucose lowering drug aside from insulin would qualify as a type2 individual seems robust. However, there may be a small number of individuals with type2 diabetes who especially in recent years received insulin only, however generally uncommon, which could lead to a misclassification in the type1 group. We have tried to minimize this problem by introducing a one year quarantine period in the beginning of our study period (see also Methods section).

Unfortunately, we did not have access to other important clinical information in risk factor control, such as lipid disorders, body mass index, smoking, physical activity, and dietary factors, and consequently we were unable to take these measures into account when estimating diabetes risk.

The Birth Registry had incomplete information on parental status, as in 4,070,681 (55.8%) cases were both parents known, whereas in 24,423 (0.3%) cases only the father was known and in 328,372 (4.5%) only the mother was known and in 2,869,359 (39,3%) of cases the registry contained no information on parents. Some insecurity may also apply to the registration of the biological father when compared to the mother. Consequently, data of relatives are lower than would be expected if data for all 7.3 million individuals were known.

6.3 Perspectives for future research

Although our data strongly indicate that genetic risk factors account for the majority of the proneness for an individual to develop diabetes, further investigation is needed to asses which genes – known or unknown – that account for the most important findings. Furthermore, although we claim that the environmental factors are secondary, this claim is based on the increased risks observed in second-degree relatives (half-siblings) and choice of spouse. This conclusion could be erroneous because we really have no direct measurement of risk factors other than the need for diabetic drugs and family relation, thus eating at the same dinner table may lead to obesity for the entire family, and this could be interpreted wrongly as a genetic disposition.

Despite the entanglement of genetic, intergenic, environmental factors, and combinations of all of them have considerable technical challenges [30], based on our findings, we consider it important to further pursue genetic components associated with diabetes.

Future studies should aim to identify genes that in combination with risk factors lead to onset of diabetes.

7 Funding

The study was funded by Aalborg University Hospital and Aalborg University with no external sponsors.

8 Duality of interest

The authors have no duality of interest to declare in the present context.

Gunnar Gislason is a minor shareholder of Novo Nordisk.

9 Contribution statement

All authors contributed to vital parts of the present paper. No author has been included as a courtesy, and all authors did actual work on the paper.

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11 Tables

Table 1: Demographics of population with onset of diabetes 1996-2012.

Family relation	At when first risk (% of all)	Diagnosed (%)	Age with 95% CI	Person years all (x100.000)	Person years diagnosed (x100.000, % of all)
Total population	7,292,835 (100.0%)	343,237 (4.7%)	59.4 (95% CI: 59.4-59.5)	1,195.72	42.05 (3.5%)
Risk if mother has diabetes	250,140 (3.4%)	15,789 (6.3%)	43.5 (95% CI: 43.3-43.6)	50.89	2.35 (4.6%)
Risk if father has diabetes	297,441 (4.1%)	15,065 (5.1%)	41.5 (95% CI: 41.3-41.7)	62.92	2.24 (3.6%)
Risk if both parents has diabetes	33,224 (0.5%)	3,201 (9.6%)	41.6 (95% CI: 41.3-42.0)	7.01	0.48 (6.9%)
Risk if full sibling has diabetes	121,357 (1.7%)	13,455 (11.1%)	44.7 (95% CI: 44.5-44.9)	25.64	1.91 (7.5%)
Risk if half sibling (common mother) has diabetes	14,881 (0.2%)	983 (6.6%)	40.0 (95% CI: 39.3-40.8)	3.13	0.14 (4.5%)
Risk if half sibling (common father) has diabetes	16,914 (0.2%)	912 (5.4%)	40.1 (95% CI: 39.3-40.9)	3.55	0.13 (3.7%)
Risk if twin has diabetes	1,704 (0.0%)	362 (21.2%)	42.8 (95% CI: 41.2-44.4)	0.34	0.05 (14.9%)
Risk if husband has diabetes	140,071 (1.9%)	14,691 (10.5%)	60.1 (95% CI: 59.9-60.3)	28.11	1.88 (6.7%)
Risk if wife has diabetes	99,600 (1.4%)	14,384 (14.4%)	62.6 (95% CI: 62.5-62.8)	17.87	1.74 (9.7%)
Risk if any familiy member has diabetes	619,746 (8.5%)	36,858 (5.9%)	43.1 (95% CI: 43.0-43.2)	129.03	5.40 (4.2%)

12 Figures

Figure 1: Flowchart of selection of study population

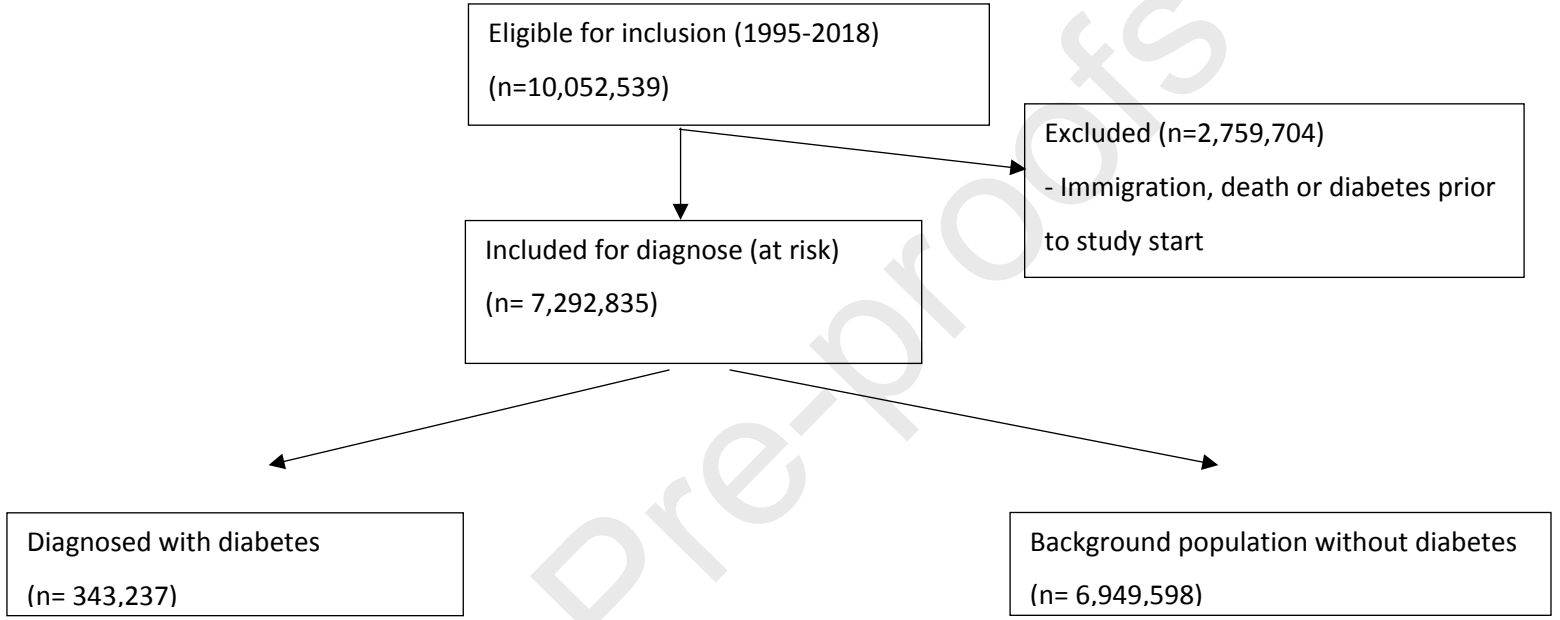

Figure 2: Risk of all types of diabetes dependent on family relation. Note that the percentage of individuals with diabetes may differ from the calculated relative risk (RR). This is due to the fact that risk estimates are calculated based on data stratified by age of diabetes onset, sex and calendar year, thus allowing a difference between calculated "raw" percentages and relative risks.

Family relation	At risk (% of all)	Diagnosed (%)	RR	95% LCL	95% UCL	P-value
Total population	7,292,835 (100.0%)	343,237 (4.7%)	.	.	.	.
Risk if mother has diabetes	250,140 (3.4%)	15,789 (6.3%)	2.06	2.02	2.10	<.0001
Risk if father has diabetes	297,441 (4.1%)	15,065 (5.1%)	1.79	1.76	1.83	<.0001
Risk if both parents has diabetes	33,224 (0.5%)	3,201 (9.6%)	3.40	3.24	3.56	<.0001
Risk if full sibling has diabetes	121,357 (1.7%)	13,455 (11.1%)	2.77	2.71	2.84	<.0001
Risk if half sibling (common mother) has diabetes	14,881 (0.2%)	983 (6.6%)	2.35	2.15	2.56	<.0001
Risk if half sibling (common father) has diabetes	16,914 (0.2%)	912 (5.4%)	1.99	1.81	2.17	<.0001
Risk if twin has diabetes	1,704 (0.0%)	362 (21.2%)	5.76	5.00	6.63	<.0001
Risk if husband has diabetes	140,071 (1.9%)	14,691 (10.5%)	1.41	1.38	1.44	<.0001
Risk if wife has diabetes	99,600 (1.4%)	14,384 (14.4%)	1.60	1.56	1.64	<.0001
Risk if any familiy member has diabetes	619,746 (8.5%)	36,858 (5.9%)	2.02	1.99	2.05	<.0001

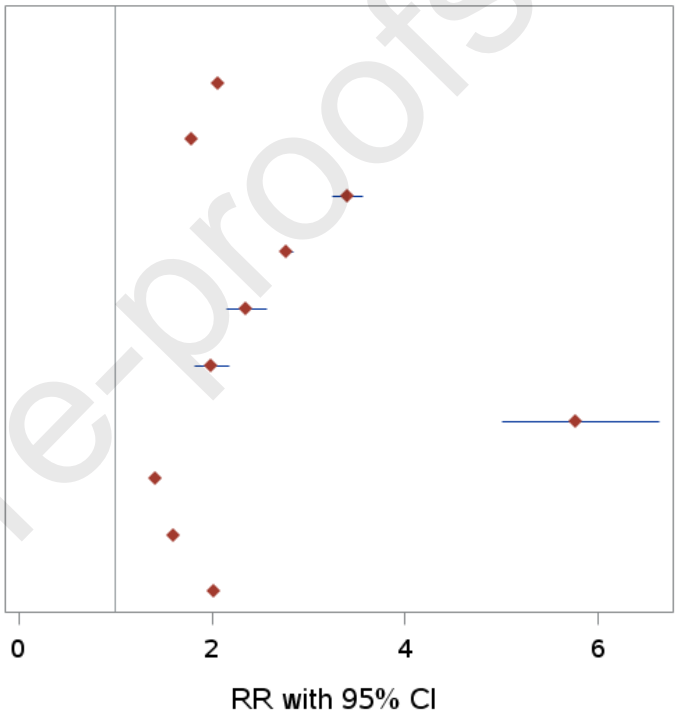

Figure 3; Risk of diabetes based on family relation for individuals with type 1 diabetes. See also main paper Figure 2 for explanations of data.

Family relation	At risk (% of all)	Diagnosed (%)	RR	95% LCL	95% UCL	P-value
Total population	7,292,835 (100.0%)	23,054 (0.3%)	.	.	.	.
Risk if mother has diabetes	9,891 (0.1%)	121 (1.2%)	4.48	3.61	5.57	<.0001
Risk if father has diabetes	13,193 (0.2%)	136 (1.0%)	3.23	2.61	3.99	<.0001
Risk if both parents has diabetes	56 (0.0%)	3 (5.4%)	9.33	1.31	66.25	0.0255
Risk if full sibling has diabetes	17,128 (0.2%)	659 (3.8%)	10.56	9.49	11.75	<.0001
Risk if half sibling (common mother) has diabetes	3,033 (0.0%)	42 (1.4%)	3.46	2.23	5.36	<.0001
Risk if half sibling (common father) has diabetes	3,185 (0.0%)	42 (1.3%)	3.14	2.03	4.87	<.0001
Risk if twin has diabetes	361 (0.0%)	46 (12.7%)	39.77	26.86	58.89	<.0001
Risk if husband has diabetes	6,591 (0.1%)	34 (0.5%)	2.08	1.36	3.19	0.0008
Risk if wife has diabetes	4,185 (0.1%)	33 (0.8%)	1.84	1.11	3.05	0.0186
Risk if any familiy member has diabetes	45,930 (0.6%)	976 (2.1%)	6.02	5.52	6.58	<.0001

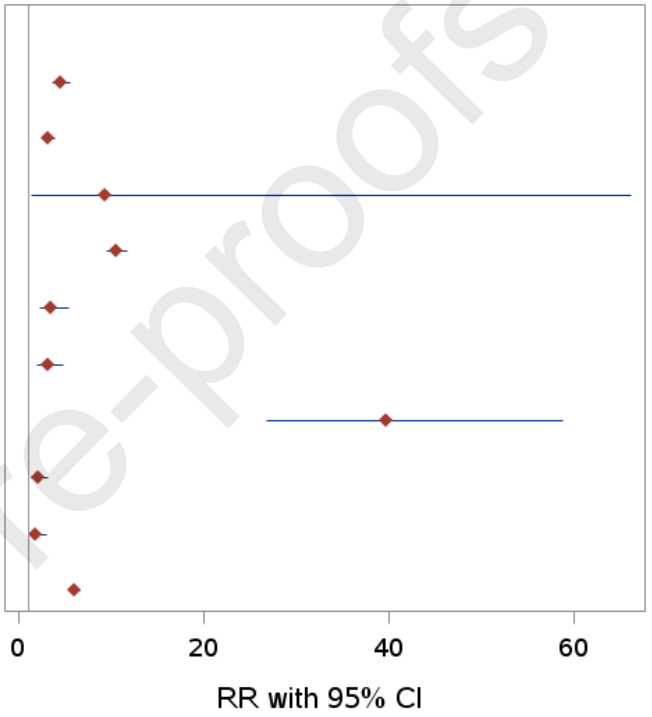

Figure 4: Scatter plot of diabnose age of person at risk, plotted towards diabetic parent age (if any).